IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Confirmation No.	:	**8534**
Appln. No.	:	10/595,385
Applicant	:	Marcus A. Horwitz, et al.
Filed	:	04/13/2008
TC/A.U.	:	**1645**
Examiner	:	Albert Mark Navarro
Docket No.	:	1951326.00019
Customer No.	:	45200
Title	:	Recombinant Intracellular pathogen Immunogenic Compositions and Methods for Use

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EXPEDITED REQUEST TO CORRECT INVENTORSHIP UNDER 37 CFR §1.48(B) AND CORRECTED FILING RECEIPT BE ISSUED

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

A request to amend inventorship under 37 CFR §1.48(b) and the fees under 37 CFR §1.17(i) associated therewith were filed in the Office on November 11, 2008. In the Office Action issued on January 29, 2009, Examiner Navarro acknowledged and accepted Applicants request to change inventorship under 37 CFR §1.132 showing that Marcus Horwitz and Gunther Harth are the sole inventors of the remaining claims. Attached please find copies of the response as filed on November 11, 2008, and the Office Action issued on January 29, 2009.

In light of the foregoing, Applicants hereby request that a Corrected Filing Receipt be issued.

The Commissioner is authorized to charge any additional fees which may be required in connection with this request to deposit account No. 503207.

Respectfully submitted,

Dated: 9/2/09

Michelle S. Glasky, Ph.D.
Registration No. 54124
CUSTOMER NUMBER: 45200

K& L GATES
1900 Main Street, Suite 600
Irvine, California 92614-7319
Telephone: (949) 253-0900
Facsimile: (949) 253-0902

Electronic Acknowledgement Receipt

EFS ID:	4269636
Application Number:	10595385
International Application Number:	
Confirmation Number:	8534
Title of Invention:	Recombinant intracellular pathogen immunogenic compositions and methods for use
First Named Inventor/Applicant Name:	Marcus A. Horwitz
Customer Number:	45200
Filer:	Louis C. Cullman/Amanda Stenson
Filer Authorized By:	Louis C. Cullman
Attorney Docket Number:	51326-00019
Receipt Date:	11-NOV-2008
Filing Date:	13-APR-2006
Time Stamp:	20:08:18
Application Type:	U.S. National Stage under 35 USC 371

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RAM confirmation Number	12106
Deposit Account	503207
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File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)

1		195132600019-RESPONSEOA8-11-08.pdf	140712 5c47f64b9876e8ed4a77def3a099d1d7d60296f2	yes	13

Multipart Description/PDF files in .zip description		
Document Description	**Start**	**End**
Amendment/Req. Reconsideration-After Non-Final Reject	1	1
Claims	2	4
Applicant Arguments/Remarks Made in an Amendment	5	13

Warnings:					
Information:					
2	Rule 130, 131 or 132 Affidavits	195132600019-DECLATATION132-11-11-08.pdf	71752 23fbe92103a17f34735ee32f3651ec3461720f8a	no	3
Warnings:					
Information:					
3	Information Disclosure Statement Letter	195132600019-IDSXMITAL-111108.pdf	101854 6fe6a53bf960c3649808425da0da254d378b9c70	no	3
Warnings:					
Information:					
4	Information Disclosure Statement (IDS) Filed (SB/08)	195132600019-IDS-111108.pdf	203816 ad4e0e5ee5cba1e24ae914cf1a2fcc1873e138e8	no	4
Warnings:					
Information:					
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5	NPL Documents	Brooks2001.pdf	792783 f6609b5f045a8c3c7c7803657cf52c4376f5ac3f	no	4
Warnings:					
Information:					
6	Fee Worksheet (PTO-06)	fee-info.pdf	30190 4a2c45268d9fa792469244db56251c4bf007c3d	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	1341107		

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New Applications Under 35 U.S.C. 111
If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371
If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office
If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

Electronic Patent Application Fee Transmittal

Application Number:	10595385
Filing Date:	13-Apr-2006
Title of Invention:	Recombinant intracellular pathogen immunogenic compositions and methods for use
First Named Inventor/Applicant Name:	Marcus A. Horwitz
Filer:	Louis C. Cullman/Maria Nadal
Attorney Docket Number:	51326-00019

Filed as Small Entity

U.S. National Stage under 35 USC 371 Filing Fees

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Miscellaneous:				
Submission- Information Disclosure Stmt	1806	1	180	180
			Total in USD ($)	**180**

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

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Title	:	Recombinant Intracellular Pathogen Immunogenic Compositions and Methods of Use

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AMENDMENT AND REMARKS

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

The Applicants submit the following Amendment and Remarks in Response to the Office Action dated August 11, 2008 in the above referenced patent application.

Amendments to the Claims are reflected in the listing of claims which begins on page **2** of this paper.

Remarks/Arguments begin on page **5** of this paper.

Submitted herewith is a declaration under 37 C.F.R. §1.132 of inventors Marcus A. Horwitz, Günter Harth and Michael V. Tullius.

Amendments to the Claims:

This listing of claims will replace all prior versions, and listings, of claims in the application:

Listing of Claims:

1.-26. (CANCELLED)

27. (CURRENTLY AMENDED) A prime-boost vaccine strategy for protecting a mammal against infection by a pathogen of the genus *Mycobacterium* comprising:

administering a first priming immunogenic composition to a vaccinee wherein said first priming immunogenic composition is a Bacille Calmette Guèrin (BCG); and

administering a second boosting immunogenic composition, after the passage of a period of time, to said vaccinee optionally in the presence of an adjuvant, wherein said second boosting immunogenic composition comprises at least one ~~is a~~ purified Mycobacteria major extracellular protein selected from the group consisting of *Mycobacterium tuberculosis* (Mtb) 23.5 kDa protein, Mtb 30 kDa protein, *Mycobacterium bovis* (MB) 30 kDa protein, MB 32A kDa protein, *Mycobacterium leprae* (ML) 23.5 kDa protein, ML 30 kDa protein, and ML 32A kDa protein; ~~and~~

wherein a protective immune response against said pathogen of the genus *Mycobacterium* is produced ~~results~~ in said vaccinee.

28. (CURRENTLY AMENDED) The prime-boost vaccine strategy according to claim 27 wherein said BCG is a recombinant BCG (rBCG) that over expresses at least one Mycobacteria major extracellular protein.

29. (CURRENTLY AMENDED) The prime-boost vaccine strategy according to claim 27 wherein said ~~Mycobacteria major extracellular protein is derived from a *Mycobacterium*~~ pathogen of the genus *Mycobacterium* is selected from the group consisting of *Mycobacterium tuberculosis* (Mtb), *Mycobacterium bovis* (MB), and *Mycobacterium leprae* (ML).

30. (PREVIOUSLY PRESENTED) The prime-boost vaccine strategy according to claim 27 wherein said purified Mycobacteria major extracellular protein is a purified recombinant Mycobacteria major extracellular protein.

31. (CANCELED) ~~The prime-boost vaccine strategy according to claim 27 wherein said purified Mycobacteria major extracellular protein is selected from the group consisting of Mtb 23.5 kDa protein, Mtb 30 kDa protein, Mtb 32A kDa protein, MB 30 kDa protein, MB 32A kDa protein, ML 23.5 kDa protein, ML 30 kDa protein and ML 32A kDa protein.~~

32. (CURRENTLY AMENDED) The prime-boost vaccine strategy according to claim 28 wherein said rBCG over expresses at least one Mycobacteria major extracellular protein selected from the group consisting of Mtb 23.5 kDa protein, Mtb 30 kDa protein, Mtb 32A kDa protein, MB 30 kDa protein, MB 32A kDa protein, ML 23.5 kDa protein, ML 30 kDa protein and ML 32A kDa protein.

33.-40. (CANCELLED)

41. (CURRENTLY AMENDED) The prime-boost vaccine strategy according to claim 28 wherein said Mycobacteria[[l]] major extracellular protein and said purified Mycobacteria[[l]] major extracellular protein are the same protein.

42. (CURRENTLY AMENDED) A prime-boost vaccine strategy for protecting a mammal against infection by a pathogen of the genus *Mycobacterium* comprising:

administering a first priming immunogenic composition to a vaccinee wherein said first immunogenic priming composition is BCG; and

administering a second boosting immunogenic composition, after the passage of a period of time, to said vaccinee wherein said second boosting immunogenic composition is purified *Mycobacterium tuberculosis* 30 kDa protein; ~~and~~

wherein a protective immune response against said pathogen of the genus *Mycobacterium* is produced ~~results~~ in said vaccinee.

43. (PREVIOUSLY PRESENTED) The prime-boost vaccine strategy according to claim 42 further comprising an adjuvant.

44. (New) The prime-boost vaccine strategy according to claim 42 wherein said BCG is a rBCG that over expresses at least one Mycobacteria major extracellular protein.

45. (NEW) The prime-boost vaccine strategy according to claim 42 wherein said pathogen of the genus *Mycobacterium* is selected from the group consisting of *M. tuberculosis*, *M. bovis*, and *M. leprae*.

46. (NEW) A prime-boost vaccine strategy for protecting against infection by a pathogen of the genus *Mycobacterium* comprising:

identifying an individual who has previously been immunized with BCG; and

administering to said individual a boosting immunogenic composition, optionally in the presence of an adjuvant, wherein said boosting immunogenic composition comprises at least one purified Mycobacteria major extracellular protein selected from the group consisting of Mtb 23.5 kDa protein, Mtb 30 kDa protein, MB 30 kDa protein, MB 32A kDa protein, ML 23.5 kDa protein, ML 30 kDa protein, and ML 32A kDa protein;

wherein a protective immune response against said pathogen of the genus *Mycobacterium* is produced in said individual.

REMARKS/ARGUMENTS

Applicants respectfully request reconsideration of the instant claims.

By the amendments, Applicants do not acquiesce to the propriety of any of the Office's rejections and do not disclaim any subject matter to which Applicants are entitled. *Cf. Warner Jenkinson Co. v. Hilton-Davis Chem. Co.*, 41 U.S.P.Q.2d 1865 (U.S. 1997).

In the Claims

Claims 1-7, 16-24, 26-32 and 41-43 are pending in this application. Claims 1-7, 16-24, and 26 have been withdrawn as the result of an earlier restriction requirement and are canceled herein. Claims 8-15, 25 and 33-40 were previously canceled. Applicants retain the right to present the canceled or withdrawn claims in one or more related applications.

Claim 27 has been amended to recite that the prime-boost vaccine strategy is for protection against infection by a pathogen of the genus *Mycobacterium* (support found in paragraph [0247] of the specification); wherein the second boosting immunogenic composition comprises at least one purified Mycobacteria major extracellular protein selected from the group consisting of *Mycobacterium tuberculosis* (Mtb) 23.5 kDa protein, Mtb 30 kDa protein, *Mycobacterium bovis* (MB) 30 kDa protein, MB 32A kDa protein, *Mycobacterium leprae* (ML) 23.5 kDa protein, ML 30 kDa protein, and ML 32A kDa protein (support found in originally filed claim 31); and that a protective immune response against the pathogen of the genus *Mycobacterium* is produced in the vaccinee (amendment solely for clarification).

Claim 28 has been amended to provide a definition of the abbreviation "rBCG."

Claim 29 has been amended to recite that the pathogen of the genus Mycobacterium is selected from the group consisting of *Mycobacterium tuberculosis* (Mtb), *Mycobacterium bovis* (MB), and *Mycobacterium leprae* (ML). Support for the amendments to claim 29 can be found in paragraph [0010] of the specification.

Claim 31 has been canceled.

Claim 32 has been amended to recite that the rBCG over expresses at least one Mycobacteria major extracellular protein. Support for this amendment can be found in paragraph [0066] of the instant specification.

Claim 41 has been amended to correct typographical errors.

Claim 42 has been amended to recite that the prime-boost vaccine strategy is for protection against infection by a pathogen of the genus *Mycobacterium* (support found in paragraph [0247] of the specification); and that a protective immune response against said pathogen of the genus *Mycobacterium* is produced in the vaccinee (amendment solely for clarification). A typographical error in the spelling of vaccinee was also corrected.

New claims 44-46 have been added. Support for new claim 44 can be found in originally filed claim 28. Support for new claim 45 can be found in paragraph [0010] of the specification. New claim 46 finds support in originally filed claim 27 and in the specification in paragraph [0066].

No new matter has been introduced as a result of the claim amendments.

Inventorship

Applicants hereby cancel claims 1-7, 16-24, and 26. As a result of this amendment, Marcus A. Horwitz and Günter Harth are the sole inventors of the subject matter of pending claims 27-32 and 41-46.

Therefore, Applicants hereby request that inventorship be amended under 37 C.F.R. §1.48(b) and that Michael V. Tullius be removed as an inventor on the instant application. The invention of Michael V. Tullius is no longer being claimed in the instant application.

Applicants enclose the fee under 37 C.F.R. 1.17(i) required for amending inventorship under 37 C.F.R. §1.48(b), and request that a Corrected Filing Receipt be issued.

35 U.S.C. §102 Rejections

I. Claims 27-32 and 41-43 have been rejected under 35 U.S.C. §102(e) as being allegedly anticipated by Horwitz *et al.* (US 6,471,967, hereinafter "Horwitz"). Office Action mailed August 11, 2008 ("OA"), page 2. Applicants respectfully disagree.

The Office stated that the rejection of claims 27-32 and 41-43 can be overcome by a showing under 37 C.F.R. §1.132 that any invention disclosed but not claimed in Horwitz was derived from the inventors of the instant application and is thus not the invention by another. OA, page 2. Applicants submit herewith a declaration under 37 C.F.R. §1.132 by inventors Marcus A. Horwitz, Günter Harth and Michael V. Tullius attesting that Marcus A. Horwitz and Günter Harth are the inventors of the prime-boost strategy, the subject matter of the pending claims and that they invented the disclosed, but not claimed, subject matter in column 15 of Horwitz.

Furthermore, the inventorship of the instant application has been amended as a result of the cancellation of the withdrawn claims. The inventors of the pending claims 27-32 and 42-46 are Marcus A. Horwitz and Günter Harth.

Therefore, in light of the foregoing, Applicants respectfully request the withdrawal of the rejection of claims 27-32 and 41-43 under 35 U.S.C. §102(e) based on Horwitz.

II. Claims 27-31 and 41-43 have been rejected under 35 USC §102(e) as being allegedly anticipated by Orme *et al.* (US 7,288,261). OA, page 3. Applicants respectfully disagree.

A claim is anticipated under 35 U.S.C. §102 only if each and every element as set forth in a claim is found, either expressly or inherently described, in a single prior art reference (MPEP §2131; *Verdegaal Bros. V. Union Oil Co. of California*, 814 F.2d, 628, 631, 2 U.S.P.Q.2d 1051 (Fed. Cir. 1987)). A claimed invention is anticipated only when it is "known to the art in the detail of the claim." *Karsten Manufacturing Corp. v. Cleveland Golf Co.*, 242 F.3d 1376, 1383 (Fed. Cir. 2001). In other words, not only must the limitations of the claim be shown in a single prior art reference, the limitations must be "arranged as in the claim." *Id.*

The instant claims are directed to a prime-boost vaccine strategy comprising a first priming immunogenic composition comprising a BCG and a second boosting immunogenic composition comprising at least one purified Mycobacteria major extracellular protein.

The Office stated that Orme "disclose of vaccine compositions for boosting immunity to mycobacteria when administered in mide [*sic*] life in a subject who has been vaccinated with BCG. Orme *et al.* further disclose that a preferred protein for boosting is Ag85A, a secreted Mycobacteria major extracellular protein having a molecular weight of 30 kDa." OA, pages 3-4. Applicants respectfully point out that Orme does not disclose that the Ag85A is a 30 kDa protein. Ag85A is a 32 kDa protein. See Table 1.

Solely to expedite prosecution, and not to acquiesce to the propriety of the rejection, Applicants have amended independent claim 27 to recite that the second boosting immunogenic composition comprises at least one purified Mycobacteria major extracellular protein selected from the group consisting of *Mycobacterium tuberculosis* (Mtb) 23.5 kDa protein, Mtb 30 kDa protein, *Mycobacterium bovis* (MB) 30 kDa protein, MB 32A kDa protein, *Mycobacterium leprae* (ML) 23.5 kDa protein, ML 30 kDa protein, and ML 32A kDa protein. Both independent claims 27 and 42 have been amended to clarify that the claimed prime-boost vaccine strategy produces a protective immune response against a pathogen of the genus *Mycobacterium* in the vaccinee.

While Orme discloses vaccine compositions for boosting immunity to mycobacteria, only one "boost" composition has been enabled as producing a protective immune response, the Ag85A, which corresponds to the 32A kDa protein of the instant disclosure (see paragraph [0176]). No other boost composition was demonstrated to increase the protection seen with BCG alone to induce a protective immune response.

A prior art publication must contain within its four corners a sufficient description to enable such a person to make the invention without an unreasonable amount of experimentation. *Advanced Display Systems Inc. v. Kent State University*, 212 F.3d 1272, 1282, 54 U.S.P.Q.2d 1673, 1679 (Fed. Cir. 2000), *cert. denied*, 532 U.S. 904

(2001). Furthermore, in *Dewey & Almy Chem. Co. v. Mimex Co.,* Judge Learned Hand emphasized the point that:

> No doctrine of the patent law is better established than that a prior patent or other publication to be an anticipation must bear within its four corners adequate directions for the practice of the patent invalidated. If the earlier disclosure offers no more than a starting point for further experiments, if its teaching will sometimes succeed and sometimes fair if it does not inform the art without more how to practice the new invention, it has not correspondingly enriched the store of common knowledge and it is not an anticipation."

124 F.2d 986, 990, 52 U.S.P.Q. 138 (2d Cir. 1942).

Persons of ordinary skill in the art are well aware that generation of a protective immune response is not a predictable art. Orme states in column 7, lines 13-59 the unpredictability of vaccines against *Mycobacterium tuberculosis* "[i]n fact it is not known if most vaccine strategies will actually work if given to people who have an existing state of immunity, measured in any of a number of ways, to Mtb." Furthermore, Orme presents further results indicating that not all vaccine compositions were effective. For example, Figure 8 of Orme depicts an experiment wherein a boost comprising culture filtrate protein (wherein only 10% of the protein mixture consisted of the Ag85 complex) was no more effective than saline in boosting immunity to *M. tuberculosis* after a prior immunization with BCG. Additionally, Orme only discloses boosting with the Ag85A protein in the presence of an immunostimulatory molecule, IL-2 (column 6, lines 25-36) and does not provide any controls for IL-2 alone as a boosting composition. Therefore it is impossible for a person of ordinary skill in the art to determine if the efficacy of Orme's boost composition is due to the Ag85A protein or to the immunostimulatory IL-2. It is well known that boosting with certain immunostimulatory molecules can induce protective immunity in individuals who had previously been immunized against certain pathogens.

Therefore, Orme does not provide an enabling disclosure for all proteins of *M. tuberculosis*, much less the claimed proteins of *M. tuberculosis*, *M. bovis* and *M. leprae* (Mtb 23.5 kDa protein, Mtb 30 kDa protein, MB 30 kDa protein, MB 32A kDa protein, ML

23.5 kDa protein, ML 30 kDa protein, and ML 32A kDa protein). Orme only provides an enabling disclosure for the Ag85A protein in the presence of a strong immunostimulatory molecule, IL-2. As a result, Orme does not anticipate the subject matter of the pending claims. Therefore, in light of the foregoing, Applicants respectfully assert that claims 27-32 and 41-46 are novel over the cited prior art and respectfully request the reconsideration and withdrawal of the rejection of these claims under 35 U.S.C. §102 based on Orme.

35 U.S.C. §103 Rejections

Claims 27-32 and 41-43 have been rejected under 35 USC §103(a) as allegedly being unpatentable over Horwitz *et al.* (PNAS 97:13853-13858, 2000, hereinafter "Horwitz 2") in view of Orme. OA, page 4. Applicants respectfully disagree.

To maintain a proper rejection under 35 U.S.C. §103, the Office must meet four conditions to establish a *prima facie* case of obviousness. First, the Office must show that the prior art suggested to those of ordinary skill in the art that they should make the claimed composition or device or carry out the claimed process. Second, the Office must show that the prior art would have provided one of ordinary skill in the art with a reasonable expectation of success. Both the suggestion and the reasonable expectation of success must be adequately founded in the prior art and not in an applicant's disclosure. Third, the prior art must teach or suggest all the claim limitations. *In re Vaeck,* 20 U.S.P.Q.2d 1438, 1442 (Fed. Cir. 1991). Fourth, if an obviousness rejection is based on some combination of prior art references, the Office must show a suggestion, teaching, or motivation to combine the prior art references ("the TSM test"). *In re Dembiczak,* 50 U.S.P.Q.2d 1614, 1617 (Fed. Cir. 1999). Following *KSR Int'l Co. v. Teleflex, Inc.*, this fourth prong of the *prima facie* obviousness analysis must not be applied in a rigid or formulaic way such that it becomes inconsistent with the more flexible approach of *Graham v. John Deere*, 383 U.S. 1, 17-18 (1966); 127 S. Ct. 1727 (2007). It must still be applied, however, as the TSM test captures the important insight that "a patent composed of several elements is not proved obvious merely by

demonstrating that each of its elements was, independently, known in the prior art." *Id.* at 1741 citing *United States v. Adams*, 383 U.S. 39, 50-52 (1966).

Presently, the Office has not established a *prima facie* obviousness case under 35 U.S.C. §103 for at least the following reasons: (1) the combination of references does not teach all of the elements of the pending claims and (2) the "obvious to try" standard cannot support the rejections. Each of these reasons is addressed in turn.

I. The Cited References do not Teach all of the Elements of the Pending Claims

A. The Instant Claims

The instant claims are directed to a prime-boost vaccine strategy for protection against infection by a pathogen of the genus *Mycobacterium*; comprising administering a first priming immunogenic composition to a vaccinee wherein said first priming immunogenic composition is a BCG (claims 27-32, 41-45) or identifying an individual who had previously been immunized with BCG (new claim 46); administering a second boosting immunogenic composition comprising at least one purified Mycobacteria major extracellular protein consisting of *M. tuberculosis* 30 kDa protein (claims 42-45) or selected from the group consisting of *Mycobacterium tuberculosis* (Mtb) 23.5 kDa protein, Mtb 30 kDa protein, *Mycobacterium bovis* (MB) 30 kDa protein, MB 32A kDa protein, *Mycobacterium leprae* (ML) 23.5 kDa protein, ML 30 kDa protein, and ML 32A kDa protein (claims 27-32, 41 and 46); wherein a protective immune response against the pathogen of the genus *Mycobacterium* is produced in the vaccinee

B. The Cited Art

1. Horwitz 2

According to the Office, Horwitz 2 discloses recombinant BCG expressing the *M. tuberculosis* 30 kDa major secretory protein. OA, page 5. The Office acknowledges that Horwitz does "not teach of administering a second boosting immunogenic composition which is a purified Mycobacteria major extracellular protein." OA, page 5.

2. Orme

The Office asserts that Orme "teach of vaccine compositions for boosting immunity to mycobacteria specifically for individuals who were previously vaccinated with BCG. OA, page 5. As discussed above, Orme teaches and suggests boosting immunity to mycobacteria in individuals previously vaccinated by BCG with *M. tuberculosis* proteins. Orme only enables production of a protective immune response by boosting with the Mtb Ag85A protein.

Therefore the combination of Horwitz and Orme does not teach or suggest the claimed prime-boost strategy wherein the boost comprises at least one purified Mycobacteria major extracellular protein selected from the group consisting of Mtb 23.5 kDa protein, Mtb 30 kDa protein, MB 30 kDa protein, MB 32A kDa protein, ML 23.5 kDa protein, ML 30 kDa protein, and ML 32A kDa protein.

II. It is not "Obvious to Try" the Claimed Invention in Light of the Prior Art References

In order to rely on the "obvious to try" standard under 35 U.S.C. §103, the Office must establish that there were a finite number of identified, predictable solutions with a reasonable expectation of success. *In re Fine*, 5 U.S.P.Q. 2d 1596, 1599 (Fed. Cir. 1988); *KSR Int'l Co. v. Teleflex.*, 127 S.Ct. 1727; *see also* Examination Guidelines, 72 Fed. Reg. at 57,529. Importantly, the expectation of success must be founded in the prior art, and not Applicants' disclosure. *In re Dow*, 5 U.S.P.Q. 2d 1529, 1531 (Fed. Cir. 1988).

As Orme himself demonstrates, not all combinations of vaccines produce protection against challenge with infectious pathogen (see Figure 8). Therefore, the behaviors of the different boosting compositions are not predictable and the obvious to try standard cannot be applied.

For all of the reasons described above, the Office has not established a *prima facie* case of obviousness of pending claims 27-32 and 41-43 over Horwitz *2* in view of Orme. The cited prior art references, in combination, do not disclose all the claim

limitations, and it is not "obvious to try" the claimed invention in light of the prior art references. The Office is respectfully requested to reconsider and withdraw the rejection of claims 27-32 and 41-43 under 35 USC §103 based on Horwitz 2 in view of Orme.

CONCLUSION

Based on the foregoing, Applicants respectfully assert that pending claims 27-32 and 41-46 are in condition for allowance and request a timely Notice of Allowance be issued in this application.

The Commissioner is authorized to charge any fee which may be required in connection with this Amendment to deposit account No. 50-3207.

Respectfully submitted,

Dated: 11 November 2008

/Michelle S. Glasky/
Michelle S. Glasky, Ph.D.
Registration No. 54,124
CUSTOMER NUMBER: 45,200

K&L GATES LLP
1900 Main Street, Suite 600
Irvine, California 92614-7319
Telephone: (949) 253-0900
Facsimile: (949) 253-0902

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

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Applicant	:	Marcus A. Horwitz *et al.*
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TC/A.U.	:	1645
Examiner	:	Navarro, Albert Mark
Docket No.	:	1951326.00019
Customer No.	:	45200
Title	:	Recombinant Intracellular Pathogen Immunogenic Compositions and Methods of Use

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Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

DECLARATION OF MARCUS A. HORWITZ, GÜNTER HARTH AND MICHAEL V. TULLIUS UNDER 37 CFR §1.132

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

We, Marcus A. Horwitz, Günter Harth and Michael V. Tullius, declare the following:

1. We are co-inventors of the above-identified patent application, Serial No. 10/595,385.

2. We have read and are familiar with the Office Action mailed 11 August 2008 pertaining to this application.

3. We understand that in the Office Action mailed 11 August 2008, the Examiner rejected claims 27-32 and 41-43 under 35 U.S.C. §102(e) as allegedly being anticipated by Horwitz *et al.* (US 6,471,967, hereinafter "Horwitz").

4. Two of us, Marcus A. Horwitz and Günter Harth, are also the inventors of Horwitz cited as prior art in the above-referenced application.

5. Marcus A. Horwitz and Günter Harth are the sole inventors of the subject matter of claims 27-32, 41-43 and new claims 44-46 of the above-referenced application.

6. The disclosure in column 15 of Horwitz referring to intradermal injection of *Mycobacterium tuberculosis* 30 kDa major extracellular non-fusion protein to guinea pigs nine weeks after immunization with BCG or rBCG30 is the work of Marcus A. Horwitz and Günter Harth and is thus not an invention by another.

6. All statements made herein of our own knowledge are true and that all statements made on information and belief are believed to be true; and further, that the statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under section 1001 of Title 18 of the United States Code, and such willful false statements may jeopardize the validity of the application or any patents issuing thereon.

7. We further acknowledge my duty of candor and good faith in dealings before the United States Patent and Trademark Office related to the above entitled application pursuant to 37 C.F.R. §1.56.

Marcus A. Horwitz

Inventor: Marcus A. Horwitz

Date 11-10-08

Inventor: Günter Harth

Date 11-10-2008

Inventor: Michael V. Tullius

Date 11-10-2008

UNITED STATES PATENT AND TRADEMARK OFFICE

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/595,385	04/13/2006	Marcus A. Horwitz	51326-00019	8534

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K&L Gates LLP
1900 MAIN STREET, SUITE 600
IRVINE, CA 92614-7319

EXAMINER	
NAVARRO, ALBERT MARK	
ART UNIT	PAPER NUMBER
1645	
MAIL DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/595,385	HORWITZ ET AL.	
	Examiner	Art Unit	
	Mark Navarro	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 November 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *27-30,32 and 41-46* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *27-30,32 and 41-46* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *11/11/08*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant's amendment filed November 11, 2008 has been received and entered. Claims 1-26, 31 and 33-40 have been cancelled, and new claims 44-46 have been added. Accordingly, claims 27-30, 32, and 41-46 are pending in the instant application.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

1. The rejection of claims 27-32 and 41-43 under 35 U.S.C. 102(e) as being anticipated by Horwitz et al is withdrawn in view of Applicants Declaration to change inventorship under 37 CFR 1.132 showing that Marcus Horwitz and Gunter Harth are the sole inventors of the remaining claims, thereby demonstrating that the patent to Horwitz is not "by another."

2. The rejection of claims 27-30 and 41-43 under 35 U.S.C. 102(e) as being

anticipated by Orme et al is maintained.

Additionally, this rejection is applied to newly added claims 44-46.

Applicants are asserting that Orme does ***not disclose*** that the Ag85A is a 30 kDa protein, rather a 32 kDa protein. Applicants conclude that Orme et al does not teach each and every limitation of the instant claims.

Applicants arguments have been fully considered but are not found to be fully persuasive.

Applicants assert that Orme does ***not disclose*** that the Ag85A is a 30 kDa protein, rather a 32 kDa protein. However, Applicants are respectfully directed to the summary section of Orme et al, specifically summary paragraph number 14, which sets forth that "Horwitz et al, 1995, claimed that Ag85 protein protected guinea pigs against aerosol TB. This study was said by the authors to demonstrate that ***immunization with the Mtb 30 kDa major secretory protein (Ag85A)***, alone or in combination with other abundant extracellular Mtb protein induced strong cell-mediated immune responses and substantial protective immunity against aerosol challenge with virulent Mtb bacilli in the highly susceptible guinea pig model of pulmonary tuberculosis." (Emphasis added). Furthermore, determination of a molecular weight is usually an approximation at best, what one of ordinary skill in the art may call a band 32 kDa, another looking at the exact same band on the exact same gel, may call the same band 30 kDa. In other words, Applicants have not shown that the M. tuberculosis major extracellular protein identified solely by a molecular weight of 30 kDa, excludes Ag85A. Given that the claims do not recite any particular structure (e.g., SEQ ID NO), the recitation of major extracellular

protein Mtb 30 kDa is deemed to fully encompass the Mtb Ag85A major extracellular protein, which was also reported to have a molecular weight of 30 kDa by those of skill in the art.

The claims are directed to a prime boost vaccine strategy for protecting a mammal against infection by a pathogen of the genus Mycobacterium comprising administering a first priming immunogenic composition to a vaccinee wherein said first priming immunogenic composition is a BCG; administering a second boosting immunogenic composition, after the passage of a period of time, to said vaccinee optionally in the presence of an adjuvant, wherein said second boosting immunogenic composition comprises at least one purified Mycobacteria major extracellular protein selected from the group consisting of Mycobacterium tuberculosis (Mtb) 23.5 kDa, Mtb 30 kDa, Mycobacterium bovis (MB) 30 kDa, MB 32 kDa, Mycobacterium leprae (ML) 23.5 kDa, ML 30 kDa and ML 32 kDa; and wherein a protective immune response against said pathogen of the genus Mycobacterium is produced in said vaccinee.

Orme et al (US Patent Number 7,288,261) disclose of vaccine compositions for boosting immunity to mycobacteria when administered in mide life in a subject who has been vaccinated with BCG. Orme et al further disclose that a preferred protein for boosting is Ag85A, a secreted Mycobacteria major extracellular protein having a molecular weight of 30 kDa. (See abstract and claims).

For reasons of record, as well as the reasons set forth above, this rejection is

maintained.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

3. The rejection of claims 27-30, 32 and 41-43 under 35 U.S.C. 103(a) as being unpatentable over Horwitz et al in view of Orme et al is maintained.

Additionally, this rejection is applied to newly added claims 44-46.

Applicants are again asserting that Orme et al only teach of a protective immune

response with Mtb Ag85A having a molecular weight of 32 kDa, not 30 kDa. Applicants further assert that in order to rely on the "obvious to try" standard, there must be a finite number of identified, predictable solutions. *KSR Intl Co. v. Teleflex.*, 127 S. Ct. 1727.

Applicants arguments have been fully considered but are not found to be fully persuasive.

First, Applicants again assert that Orme et al only teach of a protective immune response with Mtb Ag85A having a molecular weight of 32 kDa, not 30 kDa. However, this argument has been fully addressed above in paragraph number 2.

Finally, Applicants further assert that in order to rely on the "obvious to try" standard, there must be a finite number of identified, predictable solutions. However, Applicants are respectfully directed to the success achieved by Orme et al. Orme et al specifically set forth that when selecting individuals who had received BCG early in life and then administering a boost of a major extracellular Mtb protein (described to have a molecular weight of 30 kDa as set forth above) a noted rise in the level of protection was achieved. (See abstract and claims). Consequently, no obvious to try standard is necessary, the prior art actually demonstrates success.

The claims are directed to a prime boost vaccine strategy for protecting a mammal against infection by a pathogen of the genus Mycobacterium comprising administering a first priming immunogenic composition to a vaccinee wherein said first priming immunogenic composition is a BCG; administering a second boosting immunogenic composition, after the passage of a period of time, to said vaccinee

optionally in the presence of an adjuvant, wherein said second boosting immunogenic composition comprises at least one purified Mycobacteria major extracellular protein selected from the group consisting of Mycobacterium tuberculosis (Mtb) 23.5 kDa, Mtb 30 kDa, Mycobacterium bovis (MB) 30 kDa, MB 32 kDa, Mycobacterium leprae (ML) 23.5 kDa, ML 30 kDa and ML 32 kDa; and wherein a protective immune response against said pathogen of the genus Mycobacterium is produced in said vaccinee.

Horwitz et al (PNAS Vol. 97, No. 25, pp 13853-13858, December 5, 2000) teach that recombinant BCG vaccines which express the Mycobacterium tuberculosis 30 kDa major secretory protein induced greater protective immunity against tuberculosis than conventional BCG vaccines in a highly susceptible animal model. (See abstract). Horwitz et al further teach that "immune response to the 30 kDa protein may be a critical factor in protective immunity to TB." (See page 13858).

Horwitz et al do not teach of administering a second boosting immunogenic composition which is a purified Mycobacteria major extracellular protein.

Orme et al (US Patent Number 7,288,261) teach of vaccine compositions for boosting immunity to mycobacteria specifically for individuals who were previously vaccinated with BCG. (See abstract). Orme et al reports that adults vaccinated with BCG as young children become relatively unprotected. (See summary).

Given that Horwitz et al teach of the superiority of a recombinant BCG vaccine which expressed the Mycobacterium tuberculosis 30 kDa major secretory protein, and that 2) Orme et al teach of vaccine compositions for boosting the immune response to Mycobacteria, and specifically teach of the 30 kDa major secretory protein for

administration to individuals vaccinated with BCG, it would have been prima facie obvious to have incorporated the step of administering a 30 kDa major secretory protein as taught by Orme et al with the method of vaccination as taught by Horwitz et al. One would have been motivated to add the booster step in view of the teaching by Orme et al that adults vaccinated with BCG as young children become relatively unprotected.

For reasons of record, as well as the reasons set forth above, this rejection is maintained.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Mark Navarro whose telephone number is (571) 272-0861.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Robert Mondesi can be reached on (571) 272-0956. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Mark Navarro/
Primary Examiner, Art Unit 1645
January 26, 2009